Docket No. 99N - 0529

OMB No. 0910 - 0431

SUPPORTING STATEMENT

Guidance for Industry: Changes to an Approved NDA or ANDA

A. Justification

1. Circumstances of Information Collection

This information collection approval request is for a Food and Drug Administration (FDA) guidance for industry entitled "Changes to an Approved NDA or ANDA." The guidance is intended to assist applicants in determining how they should report changes to an approved New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) under section 116 of the Food and Drug Administration Modernization Act (the Modernization Act), which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes.

On November 21, 1997, the President signed the Modernization Act (Pub. L. 105-115) into law. Section 116 of the Modernization Act amended the Federal Food, Drug, and Cosmetic Act (the act) by adding section 506A (21 U.S.C. 356a), which describes requirements and procedures for making and reporting manufacturing changes to approved new drug and abbreviated new drug applications, to new and abbreviated animal drug applications, and to license applications for biological products.

Section 116 of the Modernization Act amended the Federal Food, Drug, and Cosmetic Act by adding section 506A, which includes the following provisions:

1. A drug made with a manufacturing change, whether a major manufacturing change or otherwise, may be distributed only after the applicant validates the effects of the change on the identity, strength, quality, purity, and potency of the drug as these factors may relate to the safety or effectiveness of the drug (sections 506A(a)(1) and (b) of the act). This section recognizes that additional testing, beyond testing to ensure that an approved specification is met, is required to ensure unchanged identity, strength, quality, purity, or potency as these factors may relate to the safety or effectiveness of the drug.

2. A drug made with a major manufacturing change may be distributed only after the applicant submits a supplemental application to FDA and the supplemental application is approved by the agency. The application is required to contain information determined to be appropriate by FDA and include the information developed by the applicant when "validating the effects of the change" (section 506A(c)(1) of the act).

3. A major manufacturing change is a manufacturing change determined by FDA to have substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug. Such changes include: (1) A change made in the qualitative or quantitative formulation of the drug involved or in the specifications in the approved application or license unless exempted by FDA by regulation or guidance; (2) a change determined by FDA by regulation or guidance to require completion of an appropriate clinical study demonstrating equivalence of the drug to the drug manufactured without the change; and (3) other changes

determined by FDA by regulation or guidance to have a substantial potential to adversely affect the safety or effectiveness of the drug (section 506A(c)(2) of the act).

4. FDA may require submission of a supplemental application for drugs made with manufacturing changes that are not major (section 506A(d)(1)(B) of the act) and establish categories of manufacturing changes for which a supplemental application is required (section 506A(d)(1)(C) of the act). In such a case the applicant may begin distribution of the drug 30 days after FDA receives a supplemental application unless the agency notifies the applicant within the 30-day period that prior approval of the application is required (section 506A(d)(3)(B)(i) of the act). FDA may also designate a category of manufacturing changes that permit the applicant to begin distributing a drug made with such changes upon receipt by the agency of a supplemental application for the change (section 506A(d)(3)(B)(ii) of the act). If FDA disapproves a supplemental application, the agency may order the manufacturer to cease the distribution of drugs that have been made with the disapproved change (section 506A(d)(3)(B)(iii) of the act).

5. FDA may authorize applicants to distribute drugs without submitting a supplemental application (section 506A(d)(1)(A) of the act) and may establish categories of manufacturing changes that may be made without submitting a supplemental application (section 506A(d)(1)(C) of the act). The applicant is required to submit a report to FDA on such a change and the report is required to contain information the agency deems to be appropriate and information developed by the applicant when validating the effects of the change. FDA may also specify the date on which the report is to be

submitted (section 506A(d)(2)(A) of the act). If during a single year an applicant makes more than one manufacturing change subject to an annual reporting requirement, FDA may authorize the applicant to submit a single report containing the required information for all the changes made during the year (annual report) (section 506A(d)(2)(B) of the act).

The guidance provides recommendations to holders of approved new drug and abbreviated new drug applications who intend to make postapproval changes in accordance with section 506A of the act. The guidance covers recommended reporting categories for postapproval changes for drugs, other than specified biotechnology and specified synthetic biological products. Recommendations are provided for postapproval changes in: (1) Components and composition, (2) sites, (3) manufacturing process, (4) specification(s), (5) package, (6) labeling, and (7) miscellaneous changes.

Section 506A of the act provides FDA with considerable flexibility to determine the information and filing mechanism required for the agency to assess the effect of manufacturing changes in the safety and effectiveness of the product. There is a corresponding need to retain such flexibility in the guidance on section 506A of the act to ensure that the least burdensome means for reporting changes are available. FDA believes that such flexibility will allow it to be responsive to increasing knowledge of and experience with certain types of changes and help ensure the efficacy and safety of the products involved. For example, a change that may currently be considered to have a substantial potential to have an adverse effect on the safety or effectiveness of the product may, at a later date, based on new information or advances in technology, be determined to have a lesser potential to have

such an adverse effect. Conversely, a change originally considered to have a minimal or moderate potential to have an adverse effect on the safety or effectiveness of the product may later, as a result of new information, be found to have an increased, substantial potential to adversely affect the product. The guidance enables the agency to respond more readily to knowledge gained from manufacturing experience, further research and data collection, and advances in technology. The guidance describes the agency's current interpretation of specific changes falling into the four filing categories. Section 506A of the act explicitly provides FDA the authority to use guidance documents to determine the type of changes that do or do not have a substantial potential to adversely affect the safety or effectiveness of the drug product. The use of guidance documents allows FDA to more easily and quickly modify and update important information.

Sections 506A(a)(1) and 506A(b) of the act require the holder of an approved application to validate the effects of a manufacturing change on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug before distributing a drug made with the change. Information developed by the applicant to validate the effects of the change regarding identity, strength, quality, purity, and potency is required to be submitted to FDA under section 506A(d)(3)(A). The guidance does not provide recommendations on the specific information that should be developed by the applicant to validate the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities

and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a product as they may relate to the safety or effectiveness of the product.

Sections 506A(c)(1) and 506A(c)(2) set forth requirements for changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes). Under these sections, a supplement must be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. The applicant must obtain approval of a supplement from FDA prior to distribution of a product made using the change.

Sections 506A(d)(1)(B), 506A(d)(1)(C), and 506A(d)(3)(B)(i) set forth requirements for changes requiring supplement submission at least 30 days prior to distribution of the product made using the change (moderate changes). Under these sections, a supplement must be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. Distribution of the product made using the change may begin not less than 30 days after receipt of the supplement by FDA.

Under section 506A(d)(3)(B)(ii), FDA may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved

application may commence distribution of the drug upon receipt by the agency of a supplement for the change.

Sections 506A(d)(1)(A), 506A(d)(1)(C), 506A(d)(2)(A), and 506A(d)(2)(B) set forth requirements for changes to be described in an annual report (minor changes). Under these sections, changes in the product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product must be documented by the applicant in the next annual report.

2. Purpose and Use of Information

FDA has requested emergency processing of this proposed collection of information under section 3507(j) of the PRA and 5 CFR 1320.13. The information is needed immediately to implement section 506A of the act, which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes. The use of normal information clearance procedures would likely result in the prevention or disruption of this collection of information because section 506A takes effect on November 21, 1999. The guidance provides recommendations to holders of approved new drug and abbreviated new drug applications who intend to make postapproval changes in accordance with section 506A of the act. Section 506A explicitly provides FDA the authority to use guidance documents to determine the type of changes that do or do not have a substantial potential to adversely affect the safety or effectiveness of the drug product.

Section 505 of the act requires that a new drug may not

be marketed unless the manufacturer provides FDA with scientific evidence that the drug is both safe and effective. Without the information provided by industry on the drug products they seek to market, FDA would not be able to assure the safety and effectiveness of marketed drug products. The submission of supplements are essential for FDA to assure a marketed products's continued safety and effectiveness.

3. Use of Improved Information Technology

In the mid-1980's, FDA began working with pharmaceutical sponsors to develop Computer-Assisted New Drug Applications (CANDA). CANDAs were designed to provide information (text, data, image) electronically to facilitate the review of applications. These efforts yielded valuable information but were limited because for each new drug review division sponsors tended to develop different hardware and software approaches. A reviewer might be confronted with an array of hardware, software, and review tools to conduct a review that differed between sponsors and applications. Also, CANDAs were never approved as a substitute for the archival copy, so firms were still required to submit copies.

One solution to limitations of CANDAs was an approach whereby staff responsible for a particular review discipline (eg, chemistry, clinical) worked directly with pharmaceutical sponsors to develop a consistent approach that would be applicable to all sponsors and to all review divisions. Focus on this approach has evolved into the Electronic Regulatory Submission and Review (ERSR) Program. This new initiative is intended to ensure both the electronic availability of information and the means to manipulate this information electronically to yield a review.

ERSR has been made possible by other developments. The harmonization of FDA Form 356h has ensured that NDAs, ANDAs, and Biological License Applications would contain comparable information in the same sections of the submission. The promulgation of the "Electronic Records; Electronic Signatures" final rule allowed FDA to accept electronic submissions without an accompanying paper archival copy because electronic records are equivalent to paper records and electronic signatures are equivalent to hand-written signatures provided the requirements of 21 CFR Part 11 are met and the document has been identified in the agency's public docket as being acceptable for filing. The Guidance for Industry on "Archiving Submissions in Electronic Format - NDAs" provides for the receipt and archival of electronic report forms and tabulations. Another guidance for industry on "Providing Regulatory Submissions in Electronic Format - NDAs" issued in January 1999.

ERSR is made up of a variety of projects that are in different stages of development and implementation. These projects are categorized into 3 areas: First, "Electronic Submissions" includes standards-related projects to define the format and content of regulatory submissions; written guidance for industry to follow in preparing electronic submissions; an Electronic Document Room project to accommodate the receipt, archive, and storage of electronic transmissions; an Electronic Gateway project to provide an agency-level central point for receipt of secure electronic transmissions and routing to the Centers; and scientific databases that include structured databases, reference guides, and analytical tools used by reviewers. Second, "Corporate Databases, Documentbases and Applications" includes projects under the

Electronic Document Management System and the Management Information System. Third, other electronic initiatives including technical infrastructure, technical support, and training.

ERSR will impact the underlying business processes related to regulatory submissions and reviews. Document rooms will handle electronic media rather than paper copies. Reviewers will review submissions online and generate their review documents online. Reviewers will conduct data analysis using structured databases, which combine data extracted from the submission under review as well as historical data from earlier submissions. Industry sponsors and manufacturers will experience reduced paper costs and manpower to compile paper submissions and better access to application status information through electronic mail.

4. Efforts to Identify Duplication

The information collection required as a result of section 506A does not duplicate any other information collection.

5. Involvement of Small Entities

Although new drug development is typically an activity completed by large multinational drug firms, the information collection applies to small as well as large companies submitting marketing applications. Under the Regulatory Flexibility Act, FDA regularly analyzes regulatory options that would minimize any significant impact on small entities. FDA also assists small businesses in complying with regulatory requirements.

The total savings to industry as a result of the new

supplement submission requirements would increase over time. New information and technology will allow a greater number of changes to be reported in supplements that do not require prior approval or in annual reports. In a related proposed rulemaking implementing section 116 of the Modernization Act (published June 28, 1999, 64 FR 34608), FDA certified that the proposal will not have a significant adverse economic impact on a substantial number of small entities.

6. Consequences If Information Collected Less Frequently

The requirement to report to FDA manufacturing changes establishes a reporting frequency that is dictated by the need to focus on potential problems concerning the safety and effectiveness of human drugs. Less frequent data collection would hinder early detection of such threats to the public health.

7. Consistency with the Guidelines in 5 CFR 1320.5(d)(2)

There is no inconsistency as a result of this guidance and section 506A. Any inconsistencies are related to regulatory requirements concerning supplement submission under 21 CFR 314, and are approved by OMB under OMB Control Number 0910-0001.

8. Consultation Outside the Agency

In the Federal Register of June 28, 1999 (64 FR 34660), FDA announced the availability of a draft version of this guidance. FDA received numerous public comments on the draft guidance and has considered these comments in developing the final guidance. In addition, on August 19, 1999, FDA held a public meeting to discuss and receive comments on the draft

guidance (see 64 FR 42625).

9. Remuneration of Respondents

FDA has not provided and has no intention to provide any payment or gift to respondents under these requirements.

10. Assurance of Confidentiality

Confidentiality of the information submitted under these reporting requirements is protected under 21 CFR 314.430 and under 21 CFR part 20. The unauthorized use or disclosure of trade secrets required in applications is specifically prohibited under Section 310(j) of the Act.

11. Questions of a Sensitive Nature

There are no questions of a sensitive nature.

12. Estimates of Annualized Hour Burden

Sections 506A(a)(1) and 506A(b) of the act require the holder of an approved application to validate the effects of a manufacturing change on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug before distributing a drug made with the change. Under section 506A(d)(3)(A), information developed by the applicant to validate the effects of the change regarding identity, strength, quality, purity, and potency is required to be submitted to FDA as part of the supplement or annual report. Thus, no separate estimates are provided for these sections in the table above; estimates for validation requirements are included in the estimates for supplements and annual reports. The guidance does not provide recommendations on the specific information that should be

developed by the applicant to validate the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a product as they may relate to the safety or effectiveness of the product.

Sections 506A(c)(1) and 506A(c)(2) set forth requirements for changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes). Under these sections, a supplement must be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. The applicant must obtain approval of a supplement from FDA prior to distribution of a product made using the change.

Based on data concerning the number of supplements received by the agency, FDA estimates that approximately 1,744 supplements will be submitted annually under sections 506A(c)(1) and 506A(c)(2). FDA estimates that approximately 594 applicants will submit such supplements, and that it will take approximately 120 hours to prepare and submit to FDA each supplement.

Sections 506A(d)(1)(B), 506A(d)(1)(C), and 506A(d)(3)(B)(i) set forth requirements for changes requiring supplement submission at least 30 days prior to distribution of the product made using the change (moderate changes). Under these sections, a supplement must be submitted for any

change in the product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. Distribution of the product made using the change may begin not less than 30 days after receipt of the supplement by FDA.

Based on data concerning the number of supplements received by the agency, FDA estimates that approximately 2,754 supplements will be submitted annually under sections 506A(d)(1)(B), 506A(d)(1)(C), and 506A(d)(3)(B)(i). FDA estimates that approximately 594 applicants will submit such supplements, and that it will take approximately 80 hours to prepare and submit to FDA each supplement.

Under section 506A(d)(3)(B)(ii), FDA may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug upon receipt by the agency of a supplement for the change. Based on data concerning the number of supplements received by the agency, FDA estimates that approximately 486 supplements will be submitted annually under section 506A(d)(3)(B)(ii). FDA estimates that approximately 486 applicants will submit such supplements, and that it will take approximately 80 hours to prepare and submit to FDA each supplement.

Sections 506A(d)(1)(A), 506A(d)(1)(C), 506A(d)(2)(A), and 506A(d)(2)(B) set forth requirements for changes to be described in an annual report (minor changes). Under these sections, changes in the product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength,

quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product must be documented by the applicant in the next annual report.

Based on data concerning the number of supplements and annual reports received by the agency, FDA estimates that approximately 6,929 annual reports will include documentation of certain manufacturing changes as required under sections 506A(d)(1)(A), 506A(d)(1)(C), 506A(d)(2)(A), and 506A(d)(2)(B). FDA estimates that approximately 704 applicants will submit such information, and that it will take approximately 25 hours to prepare and submit to FDA the information for each annual report.

Estimated Annual Reporting Burden

Federal Food, Drug, and Cosmetic Act Sections	Number of Respondents	Number of Responses Per Respondent	Total Annual Responses	Hours Per Response	Total Hours
506A(c)(1) 506A(c)(2) Prior Approval Supp.	594	3	1,744	120	209,280
506A(d)(1)(B) 506A(d)(1)(C) 506A(d)(3)(B)(i) CBE in 30-days Supp.	594	5	2,754	80	220,320
506A(d)(1)(B) 506A(d)(1)(C) 506A(d)(3)(B)(ii) CBE Supp.	486	1	486	80	38,880
506A(d)(1)(A) 506A(d)(1)(C) 506A(d)(2)(A) 506A(d)(2)(B) Annual Report	704	10	6,929	25	173,225
Total					641,705

There are no capital costs or operating and maintenance costs associated with this collection of information

13. Estimates of Annualized Cost Burden to Respondents

FDA's Economics Staff estimates an average industry wage rate of $50.00 per hour for preparing and submitting the information collection requirements under section 506A. This figure is an average of the following wage rates (based on the percentage of time required for each type of employee): Upper management at $70.00 per hour; middle management at $35.00 per hour; and clerical assistance at $23.00 per hour. Using the averaged wage rate of $50.00 per hour, and multiplied times the total hour burden estimated above, the total cost burden to respondents is $32,085,250.

14. Estimates of Annualized Cost Burden to the Government

Using the estimate of $50.00 per hour as the hourly wage for FDA reviewers to review supplement submissions under the proposal, and estimating that it takes an average of approximately 120 hours to review each submission, the annualized cost to FDA as a result of this proposed rulemaking would be $71,478,000 (11,913 x 120 x $50).